International Journal of Gerontology 9 (2015) 46–51

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Analysis of Medical Resource Utilization and Outcome of Inhaled Nitric Oxide in Patients Undergoing Mechanical Ventilation☆

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ARTICLE INFO

Article history:
Received 4 September 2013
Received in revised form
22 January 2014
Accepted 6 March 2014
Available online 18 March 2015

Keywords:
case mix index,
comorbidity,
nitric oxide,
utilization,
ventilators

SUMMARY

Background: Inhaled nitric oxide (iNO) is a potent selective pulmonary vasodilator, which is used in critically ill patients to improve oxygenation. It avoids systemic hypotension and ventilator-induced lung injury in patients using ventilators. This study explored the medical resource utilization and outcome, and predicted risk factors for mortality in patients using ventilators with iNO.

Methods: The database was from the National Health Insurance hospital claims data in Taiwan from 2004 to 2009. The patients using ventilators with iNO were collected and stratified by age to 20–44 years, 45–64 years, 65–74 years, and ≥ 75 years.

Results: Seven hundred and thirty ventilator patients with iNO were enrolled (63.15% male, mean age 60 years). Mechanical ventilation (MV) weaning rate was 18.25%, intensive care unit (ICU) readmission rate was 5.75%, and ICU mortality rate was 74.52%. ICU mortality rate was lower, case-mix index, MV weaning rate, and hospital costs were higher for patients aged 20–44 years and 45–64 years than in those aged 65–74 years and ≥ 75 years ($p < 0.05$). Sex, case-mix index, Charlson comorbidity index, whether MV weaning ($p < 0.001$), different age group, and implementation of tracheostomy ($p < 0.05$) were all significant risk factors in predicting mortality of patients using ventilators with iNO.

Conclusion: This study showed that the outcome differed with age in patients using ventilators with iNO.

1. Introduction

Conventional vasodilators may easily cause systemic vasodilation, which leads to hypotension; whereas inhaled nitric oxide (iNO) is a pulmonary vasodilator that selectively enters well-ventilated alveoli. There is a large affinity between NO and hemoglobin, 1500 times more than that between CO and hemoglobin. The half-life of NO is short, so it loses its activity before entering the systemic circulation. As a result, NO does not lead to systemic hypotension[1–3], but improves the V/Q (ventilation/perfusion) mismatch of patients using ventilators, reduces intrapulmonary shunts, increases arterial oxygen content, decreases the oxygen concentration of the ventilator (FiO_2), and lowers pulmonary artery hypertension[4–6]. Dellinger et al found that the survival rate and the weaning rate of 5 ppm iNO users were the highest[7]. When newborns with persistent pulmonary hypertension use iNO, the condition of oxygenation may be improved, and the treatment demand of extracorporeal membrane oxygenation may be reduced, which also decreases the expenses of hospitalization[8,9]. However, some studies found that iNO was not able to improve the condition of oxygenation, ventilator weaning rate, and prognosis in patients[10,11]; or, the improvement was observed only temporarily, and the mortality rate, length of mechanical ventilation (MV) utilization, and the number of days in the intensive care unit (ICU) were not improved[12–14].

This study explored the medical resource utilization and outcome of patient in different age groups using iNO ventilators, and predicted risk factors for mortality. Through this study, the conditions of patients using iNO ventilators will be understood further as references for future clinical applications.

☆ Conflicts of interest: The authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.ijge.2014.03.010

2. Materials and methods

2.1. Study design and patient selection

The data were provided by the National Health Insurance (NHI) Bureau from March 1, 2004 to February 28, 2009; the targets were adult patients from around Taiwan who were in the ICU using MV with iNO (NHI registration code 57025b). Variables were statistically analyzed, including patient age, sex, case-mix index (CMI), Charlson comorbidity index (CCI), mortality rate in ICU, MV weaning rate, ICU readmission rate, tracheostomy rate, hospitalization cost, antibiotics cost, number of days using iNO, number of days in ICU, number of days hospitalized, and number of days using a ventilator. The patient medical resource utilization and outcomes were analyzed. Risk factors for mortality rate in patients using MV with iNO were analyzed according to sex, age group, CMI, CCI, MV weaning rate, and tracheostomy rate.

2.2. Measurements and variables

This study categorized patients into four age groups of 20–44 years, 45–64 years, 65–74 years and ≥ 75 years. Hospitals were categorized into three levels according to their accreditation, including medical center, regional hospital, and district hospital. Most iNO patients were found in medical centers and regional hospitals, therefore, this study excluded data from district hospitals. The regional NHI branches included Taipei, Northern, Central, Southern, Kao-Ping and Eastern Branches; only the Eastern Branch had been excluded, because no patients were using iNO. For a better annual presentation, data collected between March 1, 2004 and February 28, 2005 were presented as 2004; data collected between March 1, 2005 and February 28, 2006 was presented as 2005, and so on for the remaining data.

Amongst independent variables, medical resource utilization and disease severity were assessed using CMI and CCI values. When CMI increased, it meant that the patients in the hospital were more complicated and used more resources. The CCI values were divided into four groups, 0, 1, 2, and ≥ 3. The CCI value controls the comorbidity of patients before treatment or surgery, which avoids biased efficacy assessment. A developed comorbidity and severity calibration tool may follow up the prognosis of the patients as a good indicator. There were five scores, including 0 (no event), 1, 2, 3, and 6; the higher the score, the more severe the disease[15]. MV weaning is defined when a patient using iNO leaves the ICU without carrying a mechanical ventilator. ICU readmission is defined when a hospitalized patient leaves the ICU and returns after > 24 hours. The hospitalization expenses were the total reported to the NHI. The dependent variable was patient mortality rate. Mortality was defined when the patient's status in the NHI database changed to Code 4 and Code A, and was discharged from the hospital ICU within 24 hours due to their terminal condition[16].

2.3. Statistical analyses

Access 2007, statistics analysis system (SAS), and SPSS for Windows, version 17.0 (Chicago, IL, USA) were used in this study for data conversion and analysis. Descriptive analysis, χ^2 test, and one-way analysis of variance were used to investigate the medical resource utilization and outcomes of the patients using iNO. When the mortality risk factors of patients using iNO were investigated, in order to keep the cluster effect of the hospital on the prognosis of the patients, generalized estimating equations model and logit link function were used. Under the hypothesis of the exchangeable working correlation matrix, the data were analyzed to calculate the odds ratio and 95% confidence interval[17] of each risk factor.

3. Results

This study included 730 patients using MV with iNO; the average age was 60 years and there were 461 men (63.15%) and 269 women (36.85%). The CMI was 4.63. The CCI distribution was 28.9% for 0, 29.18% for 1, 25.62% for 2 and 16.3% for ≥ 3. The tracheostomy rate was 9.86%; the antibiotics usage rate was 97.67%; and the ICU mortality rate was 74.52% (Table 1). However, when the MV weaning rate was calculated, some NHI reporting materials were missing between 2004 and 2009; after excluding some data, the total number of patients using iNO MV was 707 and the survival rate was 18.25% (129 patients).

Table 1 also shows the distribution of patients using MV with iNO, which includes 666 patients (91.23%) from medical centers and 64 patients (8.77%) from regional hospitals. On the aspect of NHI branch, the highest number of iNO users was found in Taipei Branch, and the lowest number of iNO users was found in Kao-Ping Branch; the numbers were 498 (68.22%) and 21 (2.88%), respectively (Fig. 1). Patients using MV with iNO were mostly found in medical centers, but big differences in the distribution of iNO users in various branches were found; the number of patients in the medical centers was not proportionally related to the distribution of the branches. It is predicted that the presence of facilities and the choice of physicians are related to the number of iNO users in each hospital.

Among different age groups of the patient using MV with iNO, the analysis (Table 2) of the medical resource utilization and outcomes found that, CMI, MV weaning rate and hospitalization expense of the 20–44 years age group were higher than those of the 65–74 years and ≥ 75 years groups; the antibiotics cost of 20–44 years age group was also higher than that of the ≥ 75 years age group. However, the ICU mortality rate of the 20–44 years age group was lower than that of the 65–74 years and ≥ 75 years groups; the MV of the 20–44 years age group was also lower than that of the ≥ 75 years age group. The CMI values for the three groups mentioned were 5.70, 3.14 and 3.22 ($p < 0.001$), respectively; the MV weaning rates were 40 (25.48%), 18 (12.68%, $p < 0.05$) and 16 (8.29%, $p < 0.001$), respectively; the hospitalization costs were US$25,113, US$17,596 and US$18,507 ($p < 0.05$), respectively; the antibiotics costs were US$2,415 and US$1,714 ($p < 0.05$),

Table 1
Baseline characteristics of ventilator patients with inhaled nitric oxide.

Variable	$n = 730$
Age	60 ± 19
Sex	
Male	461 (63.15)
Female	269 (36.85)
CMI	4.63 ± 4.98
CCI	
0	211 (28.90)
1	213 (29.18)
2	187 (25.62)
≥ 3	119 (16.30)
MV weaning rate[a]	129 (18.25)
Readmission ICU rate	42 (5.75)
Tracheostomy rate	72 (9.86)
Antibiotic usage rate	713 (97.67)
ICU mortality	544 (74.52)
Hospital level	
Medical center	666 (91.23)
Regional hospital	64 (8.77)

Data are presented as mean ± standard deviation or *n* (%).
[a] $n = 707$.
CCI = Charlson Comorbidity Index; CMI = case-mix index; MV = mechanical ventilation.

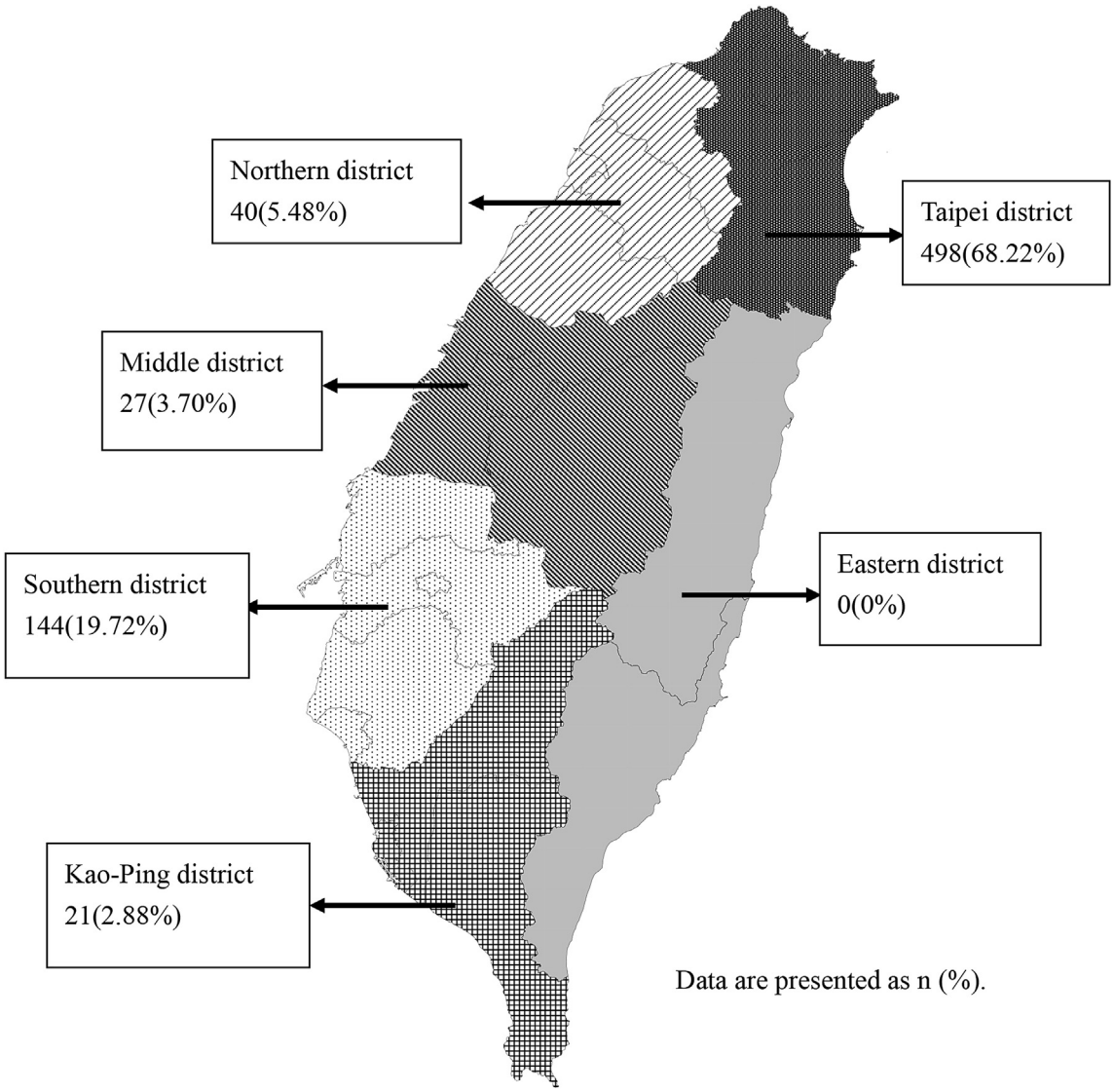

Fig. 1. Distribution of ventilator patients with iNO in different districts of the National Health Bureau in Taiwan.

respectively; the ICU mortality rates were 114 (69.51%), 117 (80.69%, $p < 0.05$), and 166 (83.00%, $p < 0.001$), respectively; the number of days using MV was 12.41 days and 18.22 days ($p < 0.05$), respectively.

The CMI and hospitalization costs of the 45–64 years age group were higher than those of the 65–74 years and ≥ 75 years groups; the MV weaning rate of the 45–64 years age group was also higher than that of the ≥ 75 years age group. However, the ICU mortality rate of the 45–64 years age group was lower than that of the 65–74 years and ≥ 75 years groups; the 0 score rate of CCI in the 45–64 years age group was lower than that in the 20–44 years and ≥ 75 years groups. In addition, the ICU readmission rate of the 45–64 years age group was lower than that of the ≥ 75 years group. The CMI values were 6.27, 3.14, and 3.22 ($p < 0.001$), respectively; the hospitalization costs were US$25,336, US$17,596, and US$18,507 ($p < 0.05$), respectively; the MV weaning rates were 25.58% (55), and 8.29% (16, $p < 0.001$), respectively; the ICU mortality rates were 66.52% (147), 80.69% (117, $p < 0.05$), and 83% (166, $p < 0.001$), respectively; the 0 scoring rates of CCI were 19.91% (44), 34.76% (57, $p < 0.05$), and 36% (72, $p < 0.05$), respectively; the ICU readmission rates were 4.07% (9) and 9% (18, $p < 0.05$), respectively. No significant difference was found in the remaining variables among the four age groups.

Fig. 2 shows ratios of the mortality rate, the MV weaning rate, the number of days using MV, and the number of days in ICU between 2005 and 2008 among patients using MV with iNO. There were too few samples of patients using MV with iNO and the weaning rate in 2004, thus, they were excluded from the final data. No significant difference was found between 2005 and 2008 for MV weaning rate, the number of days using MV, and the number of days in ICU between 2005 and 2008.

Under the hypothesis of generalized estimating equations and exchangeable working correlation matrix, Table 3 shows the logic regression of mortality risk factors in patients using MV with iNO before and after calibration. Of those, before calibration, the hospitalization cost was a significant risk factor, but it was not significant after calibration; whereas, sex, age group, CMI, CCI, MV weaning, and tracheostomy implementation were significant risk factors for patient mortality, both before and after calibration. Mortality risk in female patients was 1.56 times ($p < 0.001$) higher than that in male patients. Mortality in the ≥ 75 years age group was 1.80 times ($p < 0.05$) higher than that in the 20–44 years age

Table 2
Outcome of ventilator patients with iNO stratified by age.

Age	20–44[a]	45–64[b]	65–74	≥75
Variable	(n = 164)	(n = 221)	(n = 145)	(n = 200)
CMI	5.70 ± 5.53	6.27 ± 6.65	3.14 ± 2.94**	3.22 ± 2.36**
CCI				
0	57 (34.76)	44 (19.91)[a]	38 (26.21)	72 (36.00)[b]
1	43 (26.22)	68 (30.77)	40 (27.58)	62 (31.00)
2	41 (25.00)	66 (29.86)	38 (26.21)	42 (21.00)
≥ 3	23 (14.02)	43 (19.46)	29 (20.00)	24 (12.00)
ICU mortality	114 (69.51)	147 (66.52)	117 (80.69)*	166 (83.00)**
MV weaning rate	40 (25.48)	55 (25.58)	18 (12.68)[a]	16 (8.29)**
Readmission ICU rate	7 (4.27)	9 (4.07)	8 (5.52)	18 (9.00)[b]
Tracheostomy rate	13 (7.93)	20 (9.05)	11 (7.59)	28 (14.00)
Hospital expense (USD)	25,113 ± 18,043	25,336 ± 26,699	17,596 ± l7,706*	18,507 ± 19,451*
Antibiotics expense (USD)	2,415 ± 3,085	1,995 ± 2,374	1,719 ± 2,411	l,714 ± l,621[a]
NO duration (Day)	5.58 ± 4.83	5.61 ± 5.83	4.52 ± 3.49	5.04 ± 4.12
	5 (2~7)	4 (2~7)	4 (2~6)	4 (2~7)
ICU duration (Day)	18.29 ± 16.71	21.06 ± 29.81	17.85 ± 23.15	22.48 ± 22.48
	14.50 (7~23)	13 (5~24)	12 (5~25)	17 (9~21)
Hospital duration (Day)	28.70 ± 21.09	33.72 ± 40.92	28.03 ± 31.90	30.57 ± 34.93
	25 (12.50~39.50)	22 (12~41)	21 (8~37)	23 (12.5~37)
MV duration (Day)	12.41 ± 14.86	15.60 ± 23.52	13.41 ± 18.63	18.22 ± 23.90[a]
	8 (3.5~16)	8 (4~16)	7 (2~19)	13 (5~23)

One-way ANOVA test; post hoc tests (Bonferroni).
Data are presented as mean ± SD and median (IQR) or n (%).
*$p < 0.05$; **$p < 0.001$.
[a] Compared to 20–44.
[b] Compared to 45–64.
CCI = Charlson Comorbidity Index; CMI = case-mix index; IQR = interquartile range; MV = mechanical ventilation.

group. The risk of patient mortality decreased by 7% ($p < 0.001$) when the CMI increased by 1. The risk of mortality for patients with CCI ≥ 3 was 3.33 times ($p < 0.001$) higher than that with CCI value 0. The risk of mortality for patients not weaning from MV was 2.98 times ($p < 0.001$) higher than that in patients who were weaning from MV. The risk of mortality for patients without tracheostomy was 3.02 times ($p < 0.05$) higher than that in patients with tracheostomy.

4. Discussion

Overseas studies showed that patients using MV with iNO could not improve the weaning rate and mortality rate; it was also not related to the number of days using MV and staying in the ICU[18–20]. When the present study investigated resource utilization and outcomes of patients using MV with iNO, it was found that the overall MV weaning rate was low and the mortality rate was high,

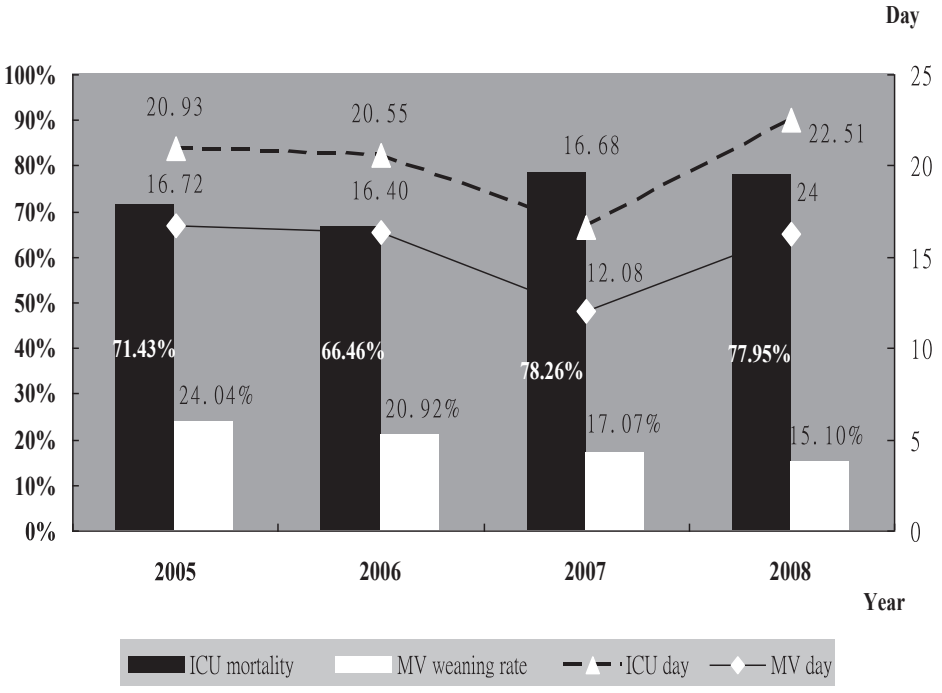

Fig. 2. Data of patients using ventilators with inhaled nitric oxide in 2005–2008.

Table 3
Predicting factors for mortality of ventilator patients with inhaled nitric oxide[a]

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p[b]
Female vs. male	1.36 (1.10–1.68)	< 0.05	1.56 (1.20–2.04)	< 0.001
Age level (y)				
20–44	Ref.		Ref.	
45–64	0.99 (0.65–1.49)	0.95	1.02 (0.66–1.58)	0.93
65–74	1.80 (0.97–3.34)	0.06	1.63 (0.94–2.82)	0.08
≥ 75	1.65 (1.05–2.59)	< 0.05	1.80 (1.14–2.83)	< 0.05
CMI	0.93 (0.90–0.95)	< 0.001	0.93 (0.90–0.96)	< 0.001
CCI				
0	Ref.		Ref.	
1	0.92 (0.71–1.19)	0.53	1.11 (0.84–1.47)	0.45
2	0.96 (0.71–1.31)	0.80	1.20 (0.79–1.82)	0.39
≥ 3	3.29 (2.05–5.29)	< 0.001	3.33 (1.88–5.88)	< 0.001
MV weaning (no vs. yes)	2.39 (1.42–4.00)	< 0.001	2.98 (1.53–5.83)	< 0.001
Tracheostomy (no vs. yes)	2.10 (1.31–3.37)	< 0.05	3.02 (1.47–6.21)	< 0.05
Hospital cost (USD)	1.0 (0.99–1.0)	< 0.05	1.0 (1.0–1.0)	0.98

[a] Multiple logistic regression using generalized estimating equations models.
[b] Adjusted for sex, age, CMI, CCI, MV weaning, tracheostomy, hospital cost.
CCI = Charlson Comorbidity Index; CI = confidence interval; CMI = case-mix index; MV = mechanical ventilation; OR = odds ratio.

which were 18.25% and 74.52%, respectively (Table 1). Further, the trend of iNO using patient between 2005 and 2008 was observed (Fig. 2). The MV weaning rates were 24.04%, 20.92%, 17.07% and 15.10%, respectively, categorized by year; the mortality rates were 71.43%, 66.46%, 78.26% and 77.95%, respectively, categorized by year; the numbers of days using MV were 16.72, 16.40, 12.08 and 16.24, respectively, categorized by year; the numbers of days staying in the ICU were 20.93, 20.55, 16.68 and 16.24, respectively, categorized by year. No significant difference was found in the MV weaning rate, mortality rate, number of days using MV, and number of days staying in the ICU among the 4 years studied. Unfortunately, this study did not compare patients using MV with and without iNO. Although no significant improvement was found in the data from those 4 years, further studies are required to clarify whether iNO treatment improves MV weaning rate and mortality rate, and whether iNO affects the number of days using MV and staying in the ICU.

The present study showed that CMI, MV weaning rate, hospitalization cost and antibiotics costs of the 20–44 years and 45–64 years age groups were higher than those of the 65–74 years and ≥ 75 years age groups; however, the ICU readmission rate and the number of days using MV in the two younger age groups were lower than in the two older age groups. Even the 0 scoring rate of CCI for the ≥ 75 years age group was higher than that for the 45–64 years age group, and the ICU mortality rates for the 65–74 years and ≥ 75 years age groups were still higher than for the two younger groups. It is suggested that the condition of the older groups was not that severe, but the mortality rate remained higher. In addition, other studies in Taiwan have been performed on the tracheostomy rate and the mortality rate of middle-aged and old-aged patients using MV. They showed that the tracheostomy rate decreased annually in the ≥ 75 years age group, but the rate and mortality were still higher than in the other younger groups[16]. This study also found that patients using iNO aged ≥ 75 years had a similar tracheostomy rate compared to other age groups, but their mortality rate was 1.80 times ($p < 0.001$, Table 3) higher than that of the 20–44 years age group.

The younger groups had a higher rate of using the medical resource utilization and better prognosis compared to the older groups. It reminds us that we may find a balance point for the older groups to maximize the medical resource utilization and obey the ethics. In 2000, implementation of the Hospice Palliative Care Act was announced for 2001; meanwhile, the Department of Health also actively promoted a “do not resuscitate” policy, which has the hope that older and end-stage patients may be transferred to a hospice ward for more supportive treatment. The policy and regulation described above may make a difference in the rate of medical resource utilization, care quality, and prognosis. It is believed that these policies and regulations may resolve the problems described above; however, whether they can be successfully implemented remains to be assessed.

Hospice palliative care is a consistent caring trend in many countries for incurable or end-stage patients, whose pain and symptoms may be controlled and relieved. Their mental, social, and spiritual aspects are taken care of, and their willingness to undergo treatment is respected, to minimize any unnecessary suffering and pain, and to optimize the quality of life with the new caring model[16].

There were some limitations in this study. First, a retrospective study using the NHI database related to the hospital registration materials may not be consistent, due to the different habits and reporting systems among the hospitals; it is possible that some data were missed. Clinically, the severity indicators are often used, such as the acute physiology and chronic health evaluation II (APACHE II) score, and biochemical tests, including arterial oxygen content and concentration; however, some data might not be filed in the NHI database. In future, if a prospective study can be performed, detailed records, clinical data, and discussions about the appropriate timing of iNO utilization may improve the oxygenation condition in patients and optimize the care quality and prognosis. The definition of MV weaning in the NHI database for long-term users differs from that in the present study (left ICU without using MV). For quality control of the existing and new MV users, no matter how long MV was used, whether 1–21, 22–63, 94 or 124 days, all patients were considered to have weaned successfully after 5 days. It is hoped that the future researchers may increase the target size and investigate the weaning rate of >5 days to match the criteria of the NHI policy and system. Lastly, for patients using mechanical ventilation with iNO, female patient mortality was 1.56 times higher than male patient mortality (Table 3). Further studies are required to clarify the outstanding questions in this study.

In summary, CMI, MV weaning rate, hospitalization cost, and antibiotics costs for the 20–44 years and 45–64 years age groups were higher than for the 65–74 years and ≥ 75 years age groups. However, the ICU mortality rate, ICU readmission rate, and the number of days using MV for the two younger age groups were lower than for the two older age groups. This suggested that the medical resource utilization and outcomes of the patients using iNO MV varied among different age groups. Unfortunately, this study did not perform biochemical tests to measure improvement of oxygenation in the patients. The timing for clinicians to apply iNO in patients to improve medical treatment remains to be established.

Acknowledgments

This research was supported by the Chi-Mei Medical Center, Tainan, Taiwan (CMFHR10264).

The study has been granted exemption from review by the Institutional Review Board of Chi Mei Medical Center (Applicant's No: 10203-E05).

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